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MAN-IN-THE-PLANT—FDA'S FAILURE TO REGULATE DECEPTIVE DRUG LABELING

REPORT

TOGETHER WITH SEPARATE VIEWS

BY THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

OF THE

COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

HOUSE OF REPRESENTATIVES

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HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D.C., December 29, 1978.

Hon. HARLEY O. STAGGERS,
Chairman, Committee on Interstate and Foreign Commerce,
Washington, D.C.

DEAR MR. CHAIRMAN: The attached report by the Subcommittee on Oversight and Investigations concerns a case study of a drug labeling practice called the man-in-the-plant and the failure of the Food and Drug Administration (FDA) to regulate this practice. The practice involves a brand-name pharmaceutical house placing a representative of their company (or man-in-the-plant) in a generic house when a brand-name product is being manufactured. Based upon the presence of this man-in-the-plant at the generic facility, the brand-name company places its name on the label inferring they are the actual manufacturer. This report examines the man-in-the-plant practice to determine whether or not the man-in-the-plant performs any function which alters the manufacturing process from that usually employed by the generic house.

The subcommittee found that brand-name firms engage in a false and misleading labeling practice which deceives the consumer. The public is led to believe that brand-name firms manufacture certain drugs when in fact the drugs are manufactured by a generic firm. The subcommittee found that the man-in-the-plant does not perform any function which alters the manufacturing process.

Moreover, the subcommittee found that the FDA was aware of this deceptive practice and has the legislative power to stop it. However FDA made a decision not to take any action to remedy this practice.

Based on this investigation, the subcommittee recommends that Congress investigate the different facets of drug marketing and sales practices. We believe Congress should know the details of these advertising and pricing practices for prescription drugs and how they affect the cost and quality of health care. We further recommend that Congress continually monitor FDA's activities to insure that the agency meets its legislative mandate to halt misleading labeling of prescription drugs.

We recommend that FDA eliminate the fictitious and deceptive man-in-the-plant practice and require companies to disclose the actual manufacturer of prescription drugs.

We hope that this report will assist our full committee and the Subcommittee on Health and the Environment in their legislative endeavors. We also hope that this report will assist the Food and Drug Administration in its efforts to properly administer the Food, Drug and Cosmetic Act.

Sincerely,

JOHN E. MOSS,
Chairman, Subcommittee on
Oversight and Investigations.

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MAN-IN-THE-PLANT—FDA'S FAILURE TO REGULATE DECEPTIVE DRUG LABELING

I. Introduction

In recent years a number of prescription drugs have become multi-source drugs. That is, they are no longer protected by patent and are being distributed and/or manufactured by a number of drug manufacturers.[1]

The advent of multi-source drugs has meant that the share of the product market of those brand-name drugs, once manufactured under patent, is now challenged by other manufacturers or distributors. With the increase in multi-source drugs, there are now some 40 States either permitting or requiring substitution of lower-cost generics for brand-name drugs.[2] There has been a marked increase in generics prescriptions filled.[3]

Despite the number of generic prescriptions being on the rise, the brand-name manufacturers still maintain a strong edge over the generic firms. And, at present physicians prescribe 90 percent of the time by brand-name.[4] There is also a big gap for yearly dollar sales between generic and brand-name firms. Purepac and Mylan, generic firms, had average sales of $16 million for 1977; Merck and Pfizer, brand-name firms had average sales of $1 billion for 1977.[5]

The brand-name firms are making efforts to insure that physicians continue prescribing and consumers continue buying their products by advertising that their product is superior.[6] At the same time, major brand-name companies are entering the generic market through the production and/or distribution of so-called branded-generics.[7] After the drug goes off patent, the companies try to claim some of the former patent holder's product market by selling either branded-generics or generics. The branded-generics, which often carry a name different than the generic, are distributed by a brand-name company, and are priced between the brand-name drug (original patent holder) and the generic.

An example of a multi-source drug is chlordiazepoxide Hcl. The innovator and former patent holder is Roche: the brand-name is Librium. Some of the firms putting out chlordiazepoxide Hcl as a branded-generic are Parke-Davis (it also carries the brand-name Promapar); and Smith Kline (under the brand-name of Sk-Lygen); Cord, a generic firm manufacturers and distributes the drug under its generic name.

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[1] Business Week, Nov. 6, 1978, p. 205.
[2] *Id.* See also Wall Street Journal, Dec. 8, 1978, p. 1.
[3] Business Week, Nov. 6, 1978, p. 205.
[4] Bond and Lean, "Sales, Promotion and Product Differentiations in Two Prescription Drug Markets", Bureau of Economics Staff Report to the Federal Trade Commission, Feb. 1977, p. 76. (Hereinafter cited as Bond and Lean).
[5] Business Week, *supra* note 1, p. 205.
[6] Statement of Senator Gaylord Nelson, "The Brand Name Drug Companies' Campaign Against Generics" before the National Conference on Generic Drugs, June 23, 1978. See also statement of Honorable Donald Kennedy, Commissioner of Food and Drug Administration, "Generic Drugs" prepared for delivery to Annual Convention, House of Delegates, New York State Medicaid Society, New York City, Oct. 23, 1978.
[7] Business Week, *supra* note 1, p. 206.

HEW has claimed that many of the generic drugs and the brand-name drugs (including the original patent holder) or branded-generic, are therapeutically equivalent.[8] Yet, the generic is often much less expensive.[9]

Critics of brand-name company practices claim the reason for the higher price of the brand-name drug is not the cost of manufacturing the drug, but the cost of promoting the drug. The brand-name firms (or research intensive firms as they often call themselves) claim the higher price is justified by the fact that they make a better product.[10] This argument that a better product is made by the brand-name firms could be mooted by the fact that many of the multi-source drugs are made by the same generic manufacturers for distribution under the label of the brand-name firms.[11]

The only information regarding the manufacturer that is now required on a drug label by the Food and Drug Administration (FDA) is that when a distributor is not the manufacturer, the qualifying phrase "manufactured for" or "distributed by" is placed before the distributor's name.[12] This type of labeling will inform the pharmacist and physicians (who happen to see the label), that this product is not made by the distributor, though it will often not give any clue as to the actual manufacturer. Some States have sought to require the disclosure of the actual manufacturer.[13] To date, the consumer ("consumer" includes the pharmacist, physicians, and patients) has been left uninformed as to the actual manufacturer, specifically, that many of the brand-name drugs or the branded-generics are made under subcontract by generic houses.[14]

The subcommittee was concerned that attempts to disclose the actual manufacturer might be affected by a labeling practice called the man-in-the-plant. This practice involves the brand-name company's placing a representative of their company (or "man-in-the-plant") in the generic house when the brand-name product is being manufactured. And, based upon the presence of this "man-in-the-plant" at the generic facility, the brand-name company places its name on the label inferring they are the actual manufacturers (the qualifying phrases "manufactured for" or "distributed by" are absent from the label).

This report will attempt to seek answers to questions concerning the "man-in-the-plant" practice and the manner in which FDA has dealt with the practice to determine:

(i) Does the "man-in-the-plant" perform any function which alters the manufacturing process from the process usually used by the generic firm?

Is the brand-name firm's name on the label misleading or deceptive?

Does this practice subvert attempts to disclose the actual manufacturer?

Does it discourage substitution of a lower-priced generic for a brand-name drug?

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[8] See Kennedy statement, *supra* note 6.
[9] See "Guide to Drug Prices", Health Cost Financing Administration, Office of Pharmaceutical Reimbursement, Department of Health, Education, and Welfare, July 1978.
[10] *Supra*, note 6.
[11] See listing of distributors and their manufacturers, pages selected from the California list of manufacturers, appendix 1.
[12] 21 C.F.R. § 201.1.
[13] See text accompanying notes 47 to 49.
[14] *Supra* note 11.

(ii) Was FDA aware of this labeling practice?
Did FDA judge it to be misleading?
Did FDA take action that was consistent with their legislative mandate?

II. Methodology

In the spring of 1978, the subcommittee undertook an investigation of the regulation of prescription drugs. As part of this investigation, the subcommittee reviewed allegations that a number of drug firms through the use of a practice known as "man-in-the-plant", placed their name on drugs actually manufactured by generic drug firms. The subcommittee had learned of these practices through participation in executive sessions of the New York State Assembly Oversight Committee chaired by Assemblyman Harvey Stelzin.[15]

We attempted to determine whether the "man-in-the-plant" performed any function which changed the standard manufacturing processes of the generic drug houses. To determine the significance of the "man-in-the-plant" in terms of differences in product quality, the subcommittee sought access to documents from the Department of Health, Education, and Welfare (HEW), and held by FDA. The documents contained information which the manufacturers are required to file with the FDA regarding their manufacturing methods and processes.[16]

Written requests to HEW for these documents went, for the most part, unanswered.[17] The subcommittee was compelled to issue a subpoena for the documents on July 27, 1978.[18] The subpoena was directed to the Secretary of Health, Education, and Welfare. It was served on August 10, 1978, approximately 2 weeks after its issuance when repeated requests and negotiations for the materials had failed.[19] The Secretary failed to meet the deadline for the materials required by the subpoena and was voted in contempt of the subcommittee at its meeting on August 16, 1978.[20]

Despite the intransigence on the part of HEW, the subcommittee continued its investigation and, on September 8 and 12, 1978, hearings were held on the "man-in-the-plant" issues.[21] The hearings focused on the role of the FDA in allowing the "man-in-the-plant" practice and the knowledge that FDA personnel had concerning "man-in-the-plant" cases which the subcommittee uncovered.

III. Summary of Findings

The subcommittee finds that—

A. Brand-name firms engage in a false and misleading labeling practice which deceives the consumer. The public is led to believe that brand-name firms manufacture certain drugs when in fact the drugs are manufactured by a generic firm. The "man-in-the-plant"

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[15] Executive sessions of the Office of Legislative Oversight and Analysis of the New York State Assembly, 1977–78.
[16] The documents contain information required by 21 U.S.C. 355.
[17] See memorandum of Chairman John E. Moss to members of the Subcommittee on Oversight and Investigations of the Committee on Interstate and Foreign Commerce, Aug. 14, 1978, in appendix 2.
[18] *Id.*
[19] *Id.*
[20] See minutes of the business meeting of the Subcommittee on Oversight and Investigations, Committee on Interstate and Foreign Commerce. (Hereinafter cited as "Meeting".)
[21] "Man-in-the-Plant—FDA's Failure to Regulate Deceptive Drug Labeling", hearings before the Subcommittee on Oversight and Investigations, Committee on Interstate and Foreign Commerce, U.S. House of Representatives, 95th Congress, 2d sess., Sept. 8 and 12, 1978. (Hereinafter cited as "Hearings.")

does not perform any function which alters the manufacturing process.

B. FDA was aware of this deceptive labeling practice and had the legislative power to stop it. However, FDA made a decision not to take any action.

C. Many of the brand-name firms claim that they make better quality drugs than the generic firms. However, the subcommittee found that many of the brand-name firms choose generic firms to manufacture their products.

D. HEW's failure to take action against the "man-in-the-plant" was contrary to their frequently stated commitment to promote lower-cost generic drugs.

E. Brand-name firms claim that they manufacture and distribute better products than the generic firms. The subcommittee knows this is untrue in some cases. We have yet to be presented with the substantiating evidence from the companies of the higher quality of their products.

F. The subcommittee found that even though FDA and HEW have contended that multi-source drugs are therapeutically equivalent, brand-named drugs are predominately prescribed over lower-cost generic drugs.

IV. Summary of Recommendations

A. The subcommittee recommends that Congress:

1. investigate the different facets of drug marketing and sales including the advertising and pricing practices for prescription drugs and how these practices affect the cost and quality of health care; and

2. continually monitor FDA's activities to insure that the agency meets its legislative mandate to stop the misleading labeling and advertising of prescription drugs.

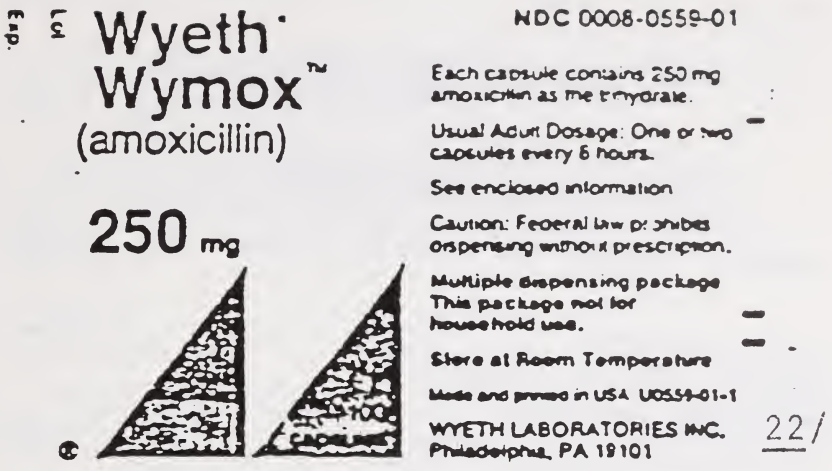
B. The subcommittee recommends that FDA:

1. promulgate regulations immediately that effectively stop the deceptive "man-in-the-plant" labeling practice; and

2. disclose the actual manufacturer of prescription drugs to eliminate the fiction that there are differences between generic and brand-name multi-source drugs.

V. Case Study—"Man-in-the-Plant"

On September 2, 1978, the subcommittee, at a public hearing, examined the "man-in-the-plant" arrangement between Wyeth Laboratories and Mylan Pharmaceutical. Wyeth sold an amoxicillin trihydrate (a semi-synthetic penicillin) under the brand-name of "Wymox". Wyeth used the following label for its marketing and distribution of the product:



The only locality stated on the label is Philadelphia, Pa. (Wyeth's place of business). In fact, the product was manufactured by a generic house, Mylan Pharmaceutical, at Mylan's manufacturing facility in Morgantown, W. Va.

In order to manufacture amoxicillin, an antibiotic, Wyeth must file an application with the FDA. An antibiotic application is known as form 6. Information required to be listed by the manufacturer in the form 6 includes: the methods and processes for the manufacture of the drug, the composition of the drug and, a listing of the key personnel involved in its manufacture.[23]

Wyeth's form 6 for Wymox states that the company will use the composition, method and processes, the personnel and the facility of the generic company, Mylan Pharmaceutical.[24] The following letter from Wyeth to FDA states that they will incorporate by reference Mylan's form 6 for the manufacture of the drug:

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[22] See appendix 3. Excerpts from Wyeth's form 6 for the manufacture of amoxicillin trihydrate. Wyeth's form 6 (with deletions by HEW) was supplied to the subcommittee by HEW pursuant to subpoena no. 95–2–75.

[23] 21 U.S.C. 355 and 21 C.F.R. § 211.101.

[24] *Supra* note 22.

WYETH LABORATORIES INC. Wyeth

January 10, 1978

Monograph No. 440.103a

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

We request that provision be made under Section 440.103a of the Antibiotic Regulations for certification of Amoxicillin Trihydrate Capsules, 250 mg and 500 mg manufactured by Wyeth Laboratories at Mylan Pharmaceuticals Inc., Morgantown, West Virginia. In support of this request, we are providing herewith the following:

1. The capsules will be manufactured, packaged, and labeled at Mylan's manufacturing laboratory in Morgantown, West Virginia in accordance with the procedures described in Mylan's approved Form 6 No. 62-067. The packaging components used will be those designated in Mylan's approved Form 6.

2. Testing will be done in accordance with the procedures described in Mylan's approved Form 6.

3. Attached herewith are letters from Mylan Pharmaceuticals Inc. authorizing reference by Wyeth Laboratories Inc. to their Antibiotic Master File and approved Form 6 No. 62-067. Also attached is a description of the qualifications of the responsible Wyeth employee.

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Certification Services

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The letter states, that the manufacturing will done be under the auspices of "the responsible Wyeth employee"—the so-called man-in-the-plant. In effect, their application for the manufacture of amoxicillin states that the drug will be made by the generic house, with the exception of the presence of Wyeth's "man-in-the-plant". FDA provided the subcommittee with the following page from the Wyeth application; expurgated from the page are the duties to be performed by the "man-in-the-plant":

[25] *Supra*, note 22.

Antibiotic Form 6, Paragraphs 3 and 4

For information required under these paragraphs, please refer to Mylan's approved Form 6 No. 62-067 and Antibiotic Master File dated August 9, 1973. Authorization for reference to these documents is attached herewith.

In addition to the personnel described in Mylan's Master File, Mr. Alex Jones, Manager, Quality Assurance Section, Wyeth Laboratories, Great Valley Laboratory or a designee with a college degree and quality assurance experience, will be present during the production of amoxicillin capsules for Wyeth Laboratories. Mr. Jones' education and experience is listed below:

B.S. Pharmacy	1951
Experience	26 years
Present Position since	1973

The duties and responsibilities of the Wyeth designee at Mylan's Morgantown, West Virginia Laboratory during the production of amoxicillin capsules for Wyeth Laboratories involve the supervision of manufacture and control activities through the responsible Mylan employees. In addition he will perform the following:

[redacted]

The subcommittee, without the assistance of HEW, acquired the missing information from the application which revealed that the duties of the "man-in-the-plant" were merely clerical in nature. According to information gathered by the subcommittee, the duties of the "man-in-the-plant" stated in Wyeth's from 6 include:

1. Checks and signs the releases of the raw materials used in the production of each Wyeth lot.
2. Checks and signs the weighing identification tickets.
3. Checks and signs the master formula sheets.
   a. Formula.
   b. Blending directions.
   c. Compaction directions.
   d. Final blending directions.
   e. Incapsulating directions.

[26] *Supra*, note 22.

4. Checks and signs the packaging directions and checks the labeling to be used.

5. Checks the sampling procedure and submits the sample for certification test.

6. Gathers all productions and testing records.

7. Checks and signs the releases for the finished product.

The form 6 illustrates that there is no substantive difference between Mylan's manufacture of amoxicillin trihydrate for itself and its manufacture of Wymox (amoxicillin trihydrate) for Wyeth. One FDA witness first raised the premise that there might be added quality assurance for brand-name products manufactured with the "man-in-the-plant" present. But, further questioning of the witness, (John Harrison, Chief Certifiable Drug Review Staff, FDA) pointed out that the clerical duties performed by the "man-in-the-plant" are performed as well by an employee of the generic firm when the generic firm is manufacturing for itself.

Ms. LEAL. Now reading through the functions that are to be performed by the man-in-the-plant, and they were read earlier, would you believe that those functions that he performs, would they make a difference in a product that is manufactured by Wyeth at Mylan Pharmaceuticals? That is, when Mylan makes amoxicillin trihydrate, is it different than when Wyeth, the brand name, makes amoxicillin trihydrate?

Mr. HARRISON. It seems to me the only difference is that we have the added assurance that Mr. Jones is checking off these things and he is in there to protect Wyeth to make sure that all these various critical steps have been performed properly.

Mr. MOSS. Does Mylan have someone who also checks to be sure these critical steps are performed?

Mr. HARRISON. When they are operating independently, yes, sir.

Mr. MOSS. In other words, these are steps that either would take care to see they were performed properly?

Mr. HARRISON. That is correct.[27]

FDA witnesses cited other cases similar to the Mylan-Wyeth arrangement. Dr. Marvin Seife, Director of Generic Drug Monographs, FDA, responding to questions from Congressman Gore (D-Tenn.) provided further examples:

Mr. GORE. We selected one example among what we believe to be many. Can you give us some other examples? I know of one involving Parke-Davis, for example, that I would like to go into in a moment.

Dr. SEIFE. In the nonantibiotic area—I will let Mr. Harrison discuss the antibiotic man-in-the-plant situations—we have several variations on the same sort of theme.

One pure instance of a man-in-the-plant involves a company called Danal Laboratories in St. Louis, Mo., which is now owned by Lemmon Pharmaceuticals of Sellersville, Pa. They have on file an application, an approved application, for the drug imipramine hydrochloride. This product is not made at the Danal premises. It is made by another facility in St. Louis called K. V. Pharmaceuticals. A person from the Danal operation is present when the imipramine is made, imipramine being an antidepressant, at K. V. That is one instance that we have.[28]

Dr. Seife listed further examples of "man-in-the-plant" arrangements in his testimony—See appendix 4.

The subcommittee found that the "man-in-the-plant" does not perform any function which alters the manufacturing process from that process usual for the generic firm.

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[27] Hearings, *supra* note 21 at pp. 88–89.
[28] *Id.* at 89.

VI. Food and Drug Administration's Labeling Policy—"Man-in-the-Plant"

A. FDA was aware of the "man-in-the-plant" problem

The Food and Drug Administration was aware of the "man-in-the-plant" problems, but failed to seek a solution. Their knowledge of the problem and their failure to limit it is demonstrated by agency correspondence and internal memoranda obtained by the subcommittee.[29] In a memo dated March 24, 1976, from Peter Barton Hutt, General Counsel to Mary S. McEniry, Assistant Director for Regulatory Affairs, Mr. Hutt wrote on the subject of "Man-in-the-Plant":

> I fully concur that this policy is obsolete (and, in my opinion, was *obsolete 10 years ago*) and should now be reconsidered.
>
> I am therefore requesting that it be placed on the agenda of a Commissioner's staff meeting with the Bureau in the near future. (Emphasis added.)[30]

In another memo by Peter Hutt to T. E. Beyers, Associate Director for Compliance dated April 16, 1976, he reiterated his concern, and questioned the legality of the practice:

> As we discussed by telephone, *it is my opinion that the policy permitting a product label to read "manufactured by" even though the product is made in an establishment owned by another company, simply because a representative of the firm identified on the label is present during manufacture, is highly questionable from a legal standpoint and seems to make no sense whatever from a policy standpoint.* Certainly, it is inconsistant with the present view of the agency, with respect to truthful and accurate labeling, and with respect to making certain that the label designates the true manufacturer of the drug. (Emphasis added.)

In fact, Hutt goes on to contend that FDA is not meeting its legislative mandate: "By declining to take legal action against activity we are in effect approving it."

Hutt concludes with the suggestion that FDA quickly promulgate a rule:

> If this policy is to be changed, it is my opinion that this can properly be done only by a proposed regulation in the Federal Register. *I would think that such a proposal could be prepared very quickly, and that it need not be lengthy or complex.* (Emphasis added.)[31]

A year later, in a memo from Mary A. McEniry to Marvin Seife, M.D., Division of Generic Drug Monographs, questions were again raised about the legality of the man-in-the-plant labeling practice. Ms. McEniry specifically raised the issue that it was a false and misleading practice, and therefore, a violation of Section 502(a) of the Food, Drug and Cosmetic Act:

> Nonetheless I conclude that if a manufacturer opts or is required by State law (this label is apparently intended to meet the requirements of several States that the manufacturer is identified on distributor labels) (sic) to include its name on the label, the name must be truthfully stated. *Thus, as the firm listed on this label is false and misleading in this respect under 502(a) and the drug is arguably misbranded under 502(b).* (Emphasis added.)[32]

In the following year, a memo dated January 13, 1977, from Mary A. McEniry to Jack L. Meyer, supervisory chemist, FDA, discussed

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[29] Memorandum supplied by FDA pursuant to written request of July 11, 1978, by Subcommittee Chairman John E. Moss to the Secretary of Health, Education, and Welfare, Joseph A. Califano, Jr. (Memorandum retained in subcommittee files.)

[30] *Id.*

[31] *Id.*

[32] *Id.*

the problem in terms of it being a subterfuge and indicated that action on "man-in-the-plant" was forthcoming.

As you are aware, we are drafting (high in-house priority) a proposed regulation that will revoke the man-in-the-plant policy but until such time as it is final, we should apply the same current policy to all manufactures. We propose to discuss leasing principles with GC and determine if any limitations or requirements can be imposed by the proposed regulation regarding the manufacturer under such arrangements. We recognize the potential for subterfuge.[33]

The subcommittee reaches the same conclusion as Ms. McEniry: that the practice is false and misleading and has the potential for subterfuge.

B. FAILURE TO STOP THE MISLEADING LABELING

FDA could have eliminated the labeling, which Congressman Gore termed "deceptive",[34] through its rulemaking authority.[35] But in 1978, a decision was made not to devote resources to resolving the problem. Mary McEniry stated in a memo dated April 17, 1978 to personnel in the Bureau of Drugs:

In the review of the Bureau of Drugs Regulatory Plan, with the Office of the Commissioner on April 13, 1978, it was decided that the Bureau would not devote resources to revising our current man-in-the-plant policy at this time. Thus for the present our policy permitting this practice will continue.[36]

The subcommittee believes that FDA was derelict in deciding at that point in time to postpone action to eliminate the deceptive labeling.

C. FAILURE TO INSPECT "MAN-IN-THE-PLANT" OPERATIONS

While some divisions of the FDA allowed the "man-in-the-plant" fiction to continue, the Division of Field Investigation (Here in after: Investigations) of FDA operated on the premise that the "man-in-the-plant" manufacture of a brand-name product was actually a generic firm product. In fact, the Investigations section of FDA did not conduct comprehensive inspections of the brand-name firm's production when they are operating under a "man-in-the-plant" situation.[37]

An example of this failure to inspect the "man-in-the-plant" operations was presented at the subcommittee hearings. This example involved the manufacture of antibiotics by Parke-Davis of Detroit, Mich., at the John D. Copanos Co. (a generic drug house) located in Baltimore, Md. Like in the *Wyeth-Mylan* case, Parke-Davis files a form 6 application with FDA claiming to manufacture amoxicillin trihydrate at their facility located at 6110 Robinwood Road, Baltimore, Md. This facility is actually owned and operated by the John D. Copanos Co. At that facility during production under the "man-in-the-plant" arrangement, the personnel and the facility are that of Copanos with the exception of Parke-Davis' "man-in-the-plant." [38] In the case of Parke-Davis at Copanos, Orton J. Cartwright, Consumer Product Safety Officer of FDA, testified that there may be one to two persons in

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[33] *Id.*
[34] Hearings, *supra* note 21 at p. 19.
[35] FDA General Counsel testified that FDA has the authority to stop the deceptive labeling. Hearings, *supra* note 21 at p. 28.
[36] *Supra* note 29.
[37] Hearings, *supra* note 21 at pp. 120–121.
[38] Hearings, *supra* note 21 at pp. 97–107. Pages selected from Parke-Davis and Co. form 6 to manufacture batches of amoxicillin trihydrate capsules in facilities leased from John D. Copanos, Inc., Baltimore, Md.

the plant.[39] Parke-Davis places its name on the label inferring that they are the manufacturer.[40]

In testifying before the subcommittee, FDA personnel who had conducted and/or supervised inspections at that plant for the last 5 years told the subcommittee that they did not conduct an inspection of the Parke-Davis operation.[41] FDA testified that they did not inspect the Parke-Davis operation although Parke-Davis maintains that the manufacturing facility is theirs.[42]

Congressman Albert Gore (D-Tenn.) questioned Mr. Cartwright concerning the belief of FDA inspectors that drug production by Parke-Davis at the Copanos facility was actually production by Copanos.

Mr. GORE. Mr. Cartwright turn to page 3 of that memorandum. This is a telephone conversation of September 8, 4 days ago. It says, "Mr. Cartwright said that in his last comprehensive *inspection he did not inspect operations other than Copanos' but may have 'observed' other operations. We tried to concentrate on Copanos. We made a conscious decision to look only at Copanos'.*"

Do you still agree with that statement?

Mr. CARTWRIGHT. *Essentially that is correct. Now, there is a reason behind that. Mr. Copanos and his firm own and operate that facility. They own the equipment, the plant, they hire the personnel and pay the personnel that work in that facility. If we find something that has to be corrected, it is up to Mr. Copanos and his company to make the corrections.*

Mr. GORE. If it is Parke, Davis' operation, it would be up to them.

Mr. CARTWRIGHT. Parke, Davis, when they operate in that plant, only has one or two people in there.

Mr. GORE. It is a fiction. They don't really have control.

Mr. CARTWRIGHT. It is still the Copanos equipment, the Copanos personnel; it is still his plant.

Mr. GORE. You say it is still Mr. Copanos' plant, but the other branches of FDA say this is a Parke, Davis plant, and, in fact, they say Parke, Davis & Co. manufacturing facility, located at 6110 Robinwood Road, Baltimore, Md. Is that the address of the plant we are talking about?

Mr. CARTWRIGHT. Yes. (Emphasis added.)

Congressman Gore concluded this exchange by characterizing the "man-in-the-plant" arrangement as a fiction—one that is continued by FDA.

Mr. GORE. This fiction is sustained by FDA. They say this is a Parke, Davis plant, and you are telling us that you have not inspected that Parke, Davis plant. You have inspected the Copanos plant, but when they go abracadabra, it is now Parke, Davis plant, after you have the presto-chango; then at that point there is no inspection. You inspect it while Copanos is operating it, but when the fiction occurs, no more inspection is needed. On the one hand, FDA says these are two different plants, and, on the other hand, you with an ample quantity of common sense, say it is the same plant; it is the same operation. This is all a fiction. There is no need to inspect it twice.

But the bottom line is FDA saying two completely contradictory things, and it is necessary for FDA to contradict itself in order to sustain this fiction, this deceptive practice which leads to a significant economic harm to the American public.[43]

The subcommittee concurs with the conclusion by Congressman Gore and finds the FDA actions to be contradictory and not in the public interest.

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[39] Hearings, *supra* note 21 at p. 129.
[40] *Id.* at pp. 97–104.
[41] *Id.* at 129.
[42] *Id.* at 96.
[43] *Id.* at 134.

VII. FDA—Contradiction in Policy Toward Generics

At the subcommittee's business meeting of August 16, 1978, Secretary Joseph A. Califano, Jr., in his prepared statement, stressed that the Department was committed to promoting lower-cost generic drugs:

First, the Commissioner of the Food and Drug Administration and I are deeply committed both to promoting the use of less expensive generic drugs and to ending the drug companies' practice of secretly marketing generic drugs produced by other manufacturers as their own, more expensive brand name products. We have taken actions to achieve both these goals.[44]

Later in his statement, Secretary Califano elaborated on his commitment, citing the Drug Regulation Reform Act as a potential remedy for the "man-in-the-plant" problem.

As you know, Mr. Chairman, both FDA Commissioner Kennedy and I are deeply concerned about promoting the use of less expensive generic drugs as an important element in our national health policy.

* * * * * * *

Our proposed Drug Regulation Reform Act of 1978, H.R. 11611, provides for a Federal drug compendium, and contains other provisions designed to facilitate the use of generic drug products.

Thus, we are firmly committed to a policy of encouraging the use of generic drugs. This hearing will help promote that policy by making the public aware that advertising claims of brand name superiority generally have no basis in fact.

Moreover, Mr. Chairman, our Drug Regulation Reform Act deals directly with the man-in-the-plant problem.

Section 147(a)(2) of that bill requires that each drug product disclose the name of the actual manufacturer on the container. Thus, the brand name manufacturers will be required to disclose publicly when their brand name products are, in fact, manufactured by generic producers.[45] (Emphasis added.)

The proposed Drug Regulation Reform Act was cited by FDA General Counsel, Richard Cooper, as a reason for the FDA's delaying any action against the "man-in-the-plant" practice. Mr. Cooper claimed that the bill would have been a cure for the "man-in-the-plant" practice and would have made their efforts against the "man-in-the-plant" moot.[46]

In fact, this problem was not addressed in FDA's proposed legislation. Under questioning by Subcommittee Chairman Moss, Mr. Cooper conceded that the drug regulation reform bill, as it was introduced, would not have changed the "man-in-the-plant" situation. That is, even with the proposed legislation, there was still a need to promulgate a rule to define when a firm is not the manufacturer by virtue of the "man-in-the-plant."

Mr. Moss. *But the area we are talking about, the one that is a crux of this, was not touched by your legislation. It is fictional manufacturing and it was not touched by your legislation. So if it was getting the attention it deserved, it should have been included specifically in the legislation and it was not.*

Mr. Cooper. Although we have authority now to deal with it in one way, the legislation would have given us an additional way to deal with it, by putting the actual name of the manufacturer on the label.

Mr. Moss. *That is only if the manufacturer was not deemed to be a manufacturer by virtue of having a man in the plant?*

Mr. Cooper. That is correct. You would have needed a definition either way.[47] (Emphasis added.)

By citing the Drug Regulation Reform Act as a potential cure for the "man-in-the-plant", the subcommittee believes that Cooper

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[44] Meeting, *supra* note 20 at p. 15.
[45] *Id.* at pp. 16–17.
[46] Hearings, *supra* note 21 at pp. 35–36.
[47] *Id.*

failed to perceive the main reason for stopping the "man-in-the-plant" practice. The "man-in-the-plant" arrangements currently allowed by FDA, would have covered-up the true manufacturer even as required by the proposed legislation. In fact, FDA's highest ranking drug regulatory official stated that the "man-in-the-plant" arrangements would be on the rise because they could be used to subvert new State laws requiring the listing of the actual manufacturer.

In a memo dated December 15, 1976, from the Director of Regulatory Affairs for the Bureau of Drugs, Mary McEniry, to Marvin Seife, M.D., Director of Generic Drug Monographs for FDA, such an assumption was put forward.

> We can only speculate as to why Mylan wishes to declare Greenbrier as the manufacturer if in fact the drug was manufactured by the parent firm Mylan. *However, this may be a situation that we will be frequently encountering with the advent of State laws requiring the identification of the manufacturer on distributor labels.* General Counsel has concurred in this response.[48] (Emphasis added.)

The States' attempts to disclose the actual manufacturer have in fact been thwarted by the "man-in-the-plant" practice. The California list of actual manufacturers is an example of a State list where the companies manufacturing under the "man-in-the-plant" arrangement are listed as the actual manufacturers.[49] Specifically, it lists Parke-Davis as the manufacturer of ampicillin where the subcommittee received documents and testimony that the drug was actually manufactured by John D. Copanos, Inc., Baltimore, Md.

The "man-in-the-plant" practice has thwarted the State's attempts to disclose the actual manufacturer—which would in many cases reveal that the "better" brands are actually made by the generic firms. It also would have made legislation requiring the actual manufacturer on the label ineffective.

Even though Secretary Califano cited the Department's commitment to lower-cost generics, the Department made an overt decision not to take any action to stop a false and misleading practice.

VIII. The Subcommittee's Investigation and Hearings Did Help the FDA Focus on the Problem

Although FDA Commissioner Donald Kennedy had testified that the "man-in-the-plant" practice was a widespread practice,[50] it was not until the subcommittee subpoenaed information on the "man-in-the-plant" from HEW that they attempted to catalogue some of the "man-in-the-plant" schemes. In the subcommittee meeting of August 16, 1978, Secretary Califano presented a list of associated manufacturers [51] which showed some of the "man-in-the-plant" relationships. This list had been requested by the subcommittee.

> Mr. Moss. Have you brought with you the materials called for by that subpena No. 95–2–75?
>
> Secretary Califano. Mr. Chairman, I have some of those materials. I can describe them briefly, and I also would like to make a few comments. I shall not do that now but I will describe the material if I may.

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[48] *Supra* note 29.

[49] See appendix 1, pages selected from California list of manufacturers.

[50] "Competitive Problems in the Drug Industry", hearings before the Subcommittee on Monopoly and Anticompetitive Activities, Select Committee on Small Business, U.S. Senate, 95th Cong., 1st Sess., November 14, 15, and 16, 1977 at p. 16463.

[51] Associated manufacturer is a term used by FDA to describe a firm who is subcontracted by another for part or all of the manufacture of a drug. Hearings, *supra* note 21 at p. 28.

I have brought with me a preliminary list containing all the information that we have been able to compile since the few days of receiving the subcommittee's subpena.

Shown on this list we have the brand name manufacturer, the drug involved, and the associated manufacturer who may be manufacturing the drug for the better known company. Inasmuch as work on this list began only this week, it is not complete. I would like to submit that to the subcommittee.[52] (Emphasis added.)

The FDA's General Counsel provided testimony that the information presented at the hearings might convince FDA to devote resources to the problem:

Mr. Cooper. I think the difficulty is not, as I have indicated, any lack of authority. We need to think the problem through and come up with a solution. It can be done.

Mr. Moss. How long do you need to think the problem through?

Mr. Cooper. That is a matter of devoting resources to it.

Mr. Moss. On this record it is 15 years. It is important. It continues to burden the American people with additional costs justified on a totally false premise of superiority of product. What in the name of God does it take to convince you that it should be looked at?

Mr. Cooper. These hearings might have that effect.[53]

On September 12, 1978, Secretary Califano, in a letter to Chairman John E. Moss (D-Calif.), reaffirmed his commitment that FDA would soon publish a notice for proposed rulemaking to address the "man-in-the-plant" issue.[54] On October 3, 1978, a proposed rule was published in the Federal Register. This proposed rule which is intended to limit the deceptive labeling is now subject to public comment.[55] And, most recently, the Commissioner of FDA announced a change in the inspection policy for companies operating under the "man-in-the-plant" arrangement.[56]

The subcommittee believes that the Food and Drug Administration must stop the deceptive "man-in-the-plant" labeling practice. FDA can and should take steps to make information regarding the actual manufacturer available to the public. Such a vehicle for making this information available would be a list of actual manufacturers not unlike the California list.[57]

The subcommittee in recognizing the necessity for disclosure of this information has requested that FDA review the California list of actual manufacturers and verify that information since FDA records are not available to the States. States which do not have information regarding the "man-in-the-plant" could be informed of the actual manufacturers.

Finally, it is important to note that until the "man-in-the-plant" labeling practice is eliminated by FDA, there cannot be complete assurance that a list of manufacturers does not include distributors shown as manufacturers.

IX. Promoters of Brand Name Companies Make Claims of Better Quality

The subcommittee believes that a number of industry claims should be addressed.

(1) "Brand-name companies make better drugs".

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[52] Meeting, *supra* note 20 at p. 5.

[53] Hearings, *supra* note 21 at pp. 34–35.

[54] *Id.* at p. 135 for a copy of the letter.

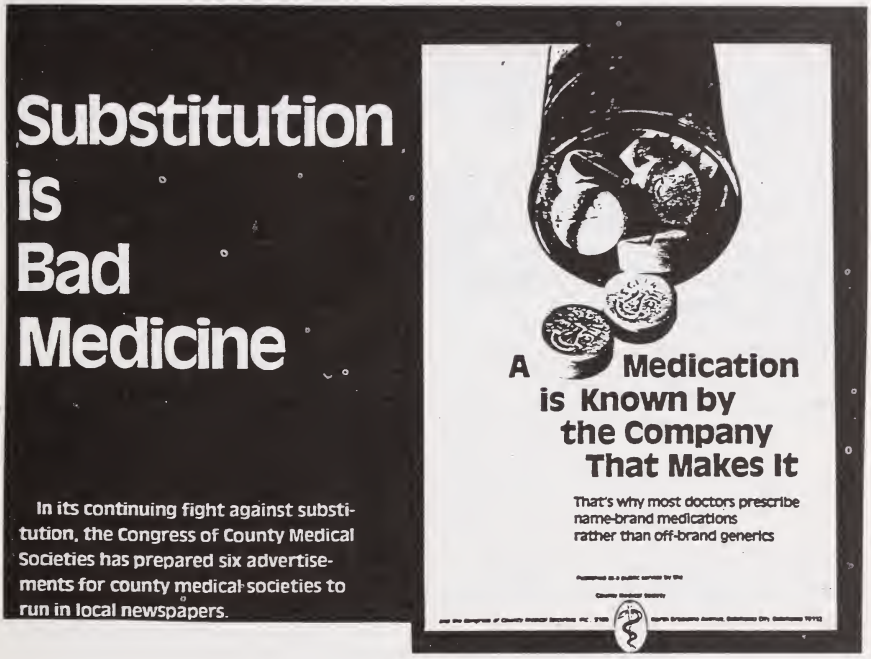
[55] See Federal Register, Vol. 23, No. 192, pp. 45614–45619.

[56] In a letter from FDA Commissioner Donald Kennedy to Chairman John E. Moss, dated Oct. 23, 1978, Commissioner Kennedy announced that FDA changed their procedure for inspection of drug manufacturing facilities to include inspection of all firms using a facility. Copy of the letter is in the subcommittee files.

[57] *Supra* note 49.

One promoter of this premise is the Congress of County Medical Societies.[58] They have waged a strong campaign against the substitution of generics for brand-name drugs.[59]

One vehicle for their campaign is their magazine Private Practice which is distributed at no charge to physicians throughout the country. An example of their campaign is the following insert in Private Practice which illustrates a poster they suggest physicians should place in their offices:



The magazine insert does not mention the man-in-the-plant practice or the fact that many brand-name firms have their drugs made by generic firms.[60] The Pharmaceutical Manufacturers Association has claimed that the brand-name products being produced by the generic firm have the benefit of special know-how of the brand-name firm and have greater quality assurance than the generic products made at the same facility.[61] One would be hard-pressed to claim that the Wyeth product benefits from special know-how or greater quality assurance due to the presence of Wyeth's man-in-the-plant who performs clerical duties. He performs clerical duties that are performed by a representative of the generic firm when they are making the product for themselves.[62]

Where there is no man-in-the-plant and the brand-name company does not claim to be the manufacturer, the brand-name company marketing the drug may claim that their specifications are somewhat different and therefore superior to the drug the generic firm is manufacturing for itself. Testimony from a FDA witness knowledgeable

[58] The Congress of County Medical Societies is an association headed by Francis A. Davis, M.D., its headquarters are in Oklahoma City, Okla.
[59] *Supra* note 50 at pp. 16158–16528.
[60] Private Practice, June 1978 at p. 80.
[61] See PMA Newsletter, Sept. 18, 1978.
[62] Hearings, *supra* note 21 at pp. 88–89.

about product specifications disagreed: (The testimony revolved around Barr Laboratories—a generic firm and Lederle—a brand-name company)

Dr. SEIFE. Getting back to Lederle, Lederle contracted for many drugs with Barr Laboratories and supplements were submitted by Barr Laboratories for Lederle to allow Lederle to become a distributor. These were processed.

Now on every one of the medicine containers for Lederle Laboratories, it states "Made to the Specification of Lederle Laboratories, Pearl River, N.Y., by Barr Laboratories, Northvale, N.J."

Now in each instance we have written to Barr Laboratories and said, "What are these special specifications other than you have in your application that Lederle Laboratories claim? You are the applicant holder." And in each instance they did not vary. The specifications were exactly the same, so this is something I have seen with several companies who get into the generic line.

I stand behind Barr's applications. I personally approve them. I know that they are good products, and I know they are distributed widely. Lederle also puts out an excellent line.[63]

The subcommittee believes that the functions performed by the man-in-the-plant do not change the quality of a drug. The subcommittee has not completed its investigation of the claims by brand-name companies that their products are superior to those produced by the generic firms. The subcommittee believes that this is a fruitful area for future investigation.

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[63] *Id.* at 117.

SEPARATE VIEWS OF THE HONORABLE JAMES M. COLLINS, M.C.

I agree with the recommendations contained in the report, because I believe as does the majority that labels on drugs should show who actually manufactured the product. I do have some difficulty with other aspects of the report which could lead one to conclude that all generic drugs are as good as the comparable brand-name drugs. That fact has never been established and, in fact, there is evidence quite to the contrary.

I feel sure that some generics are as good as some brand names, but which ones and how many, I have no idea. Thus, I believe that we should approach this issue of substitution of generics for brand names with considerable trepidation.

I also believe that too much emphasis has been placed in this debate, concerning generics versus brand names, on the issue of chemical equivalency, when the real issue, in my mind, is are the drugs therapeutically equivalent. In my view, chemical equivalency and therapeutic equivalency are not synonymous. Lowering the costs that the consumer pays is an important consideration, but a more important consideration is whether or not the patient gets better quicker or at all if the cost is made the primary consideration.

Another of my major concerns is that this exuberant movement to generics is going to do serious damage to new drug research in this country. The simple facts are that generic drug houses have no research and development budget, for they are manufacturing already approved drugs. The generic houses have for the most part no massive distribution system to get the drugs to places where the patient is in a position to buy them. These costs are borne and will continue to be borne by the brand name houses, consequently, drugs sold by brand name houses are necessarily higher in cost.

If this issue of substitution is pushed too rapidly without full knowledge of the consequences, then the results would be a total disservice to the American public. If generics are sold simply on the basis of cost and chemical equivalency without respect to therapeutic equivalency, what will be the economic consequences to the brand name houses and the consequences to the patient. First, the patient may not be aided to the same degree as he would have been if he had purchased the brand name drug, and second, if sales by brand name houses are hurt, they will not have the same degree of financial resources to support research on new drug development which is a costly and terribly time-consuming undertaking. If brand name houses have less revenue coming in, then they are going to have to cut costs and, I fear, loss of revenue for the research and development. This consequence has been completely overlooked in the report.

The report does not make a finding that all generic drugs are the therapeutic equivalent of all chemically equivalent brand names. But this point is not emphasized, and I think that it should be in the interest of legitimate consumer protection. On this very point, there was introduced into our hearing record the testimony of Mr. Edward A. Cohen, the President of Barr Laboratories, a generic house, before the New York State Assembly's Standing Committee on Consumer Affairs and Protection.

In that testimony Mr. Cohen said the following:

> Mr. COHEN. Well, I would add to that *that there are many generic drugs on the market which I would not give my family.*
>
> Mr. HADDAD. Would you explain that to me?
>
> Mr. COHEN. Just what I said. In the case of Barr, where I'm producing the product.
>
> The CHAIRMAN. That's because you're a quality house.
>
> Mr. COHEN. That's correct.
>
> Mr. HADDAD. You would have no objection to a generic drug if it were produced by a qaulity house, a house as good, as clean, as effective as Barr.
>
> Mr. COHEN. Yes. I'll go further. I have no hesitancy in taking a generic drug which was marketed by Smith Kline & French or Lederle which had dual labeling on it because I would rely on the quality control procedures that are superimposed on the generic company.
>
> Mr. HADDAD. You mean there are generics being sold today that are unsafe and ineffective?
>
> Mr. COHEN. I'm not saying that.
>
> Mr. HADDAD. You said it.
>
> Mr. COHEN. *No. I'm saying I wouldn't give it to my loved ones.* (Emphasis Added)

What Mr. Cohen is saying in effect is that certain generic drugs are of good quality, but that others are not. This is exactly my point. I do not want to see "willy-nilly" substitution of good brand name products for generic products of possibly less quality simply because the generics cost less.

One of the major failings of this investigation is that we did not take any testimony from drug manufacturers, either generic or brand name. I believe that we should have before issuing a report which in part deals with the question of "sameness."

APPENDIX 1

PAGES SELECTED FROM THE CALIFORNIA LIST OF MANUFACTURERS

Manufacturer disclosure

In light of the passage of drug product selection legislation in California, it is imperative that pharmacists be supplied with the identity of the actual manufacturer of all drug products. This is dictated not only by reason but by state law.

It has come to CPhA's attention, however, that not all pharmaceutical manufacturers are complying with the law — specifically, the manufacturer disclosure requirements in Section 10386 of Title 17 of the California Administrative Code. This section requires that the "name and place of business of the manufacturer who mixed the final ingredients and the manufacturer who encapsulated or tableted the finished dosage form" appear in the labeling of any product manufactured after June 1, 1974. In addition, even when this information is provided, the pharmacist must purchase the product before he can obtain it.

To resolve these problems, CPhA in a five-part series in 1973 and '74 published lists of the actual manufacturers of common drug products sold in California. On Aug. 16 of last year we sent this list to the manufacturers to be updated. On these pages is the compilation of the latest information provided to the Association in reply to that request. (The distributor of each drug appears on the left, the manufacturer on the right.)

AMINOPHYLLINE 100 & 200 mg Tabs

Columbia Medical Co.	Richlyn Labs
Interstate Drug Exchange[4]	Blue Cross or Richlyn Labs
Invenex Pharm.	Invenex Pharm.
Ladco Labs	Richlyn Labs
Pasadena Research Labs*	Richlyn Labs
Stanlabs	Stanlabs
Stayner Corp.*	Stayner Corp.
United Pharm.	Richlyn Labs
West-ward	West-ward

AMITRIPTYLINE HCl 25 mg Tabs

Hoffman-La Roche	Hoffman-La Roche
Merck Sharp & Dohme	Merck Sharp & Dohme

AMPICILLIN ANHYDROUS

Wyeth Labs*	Wyeth Labs

AMPICILLIN TRIHYDRATE 250 mg Caps

American Pharm. Co.*	Biocraft Labs or Zenith Labs
American Quinine Prod.*	Zenith Labs
B.F. Ascher & Co.*	International Labs
Averst Labs.* Penbritin	Beecham Labs
Beecham Labs	Beecham Labs
Biocraft[1]	Biocraft Labs
Bristol Labs*	Bristol Labs
H.R. Cenci Labs	Biocraft Labs
Columbia Medical Co.	Biocraft Labs
Consolidated Midland Corp.*	Biocraft Labs
ICN Pharm.*	International Labs
Ladco Labs	Chromalloy Pharm.
Laderle Labs. Alpen	Beecham Pharm.
McKesson Labs	Mylan Pharm.
Parke-Davis & Co.	Parke-Davis & Co.
Pfipharmecs	Beecham Labs
Phillips Roxane Labs	Biocraft Labs
Rachelle Labs	International Labs
Rexall Drug Co.[1]	Mylan Pharm.
Sheraton Labs	Mylan Pharm. or Chromalloy Pharm.
Sherry Pharm.*	Zenith Labs
Smith Kline & French Labs	Bristol Labs
E.R. Squibb & Sons	E.R. Squibb & Sons
Stayner Corp.*	International Labs
Towne, Paulsen & Co.	International Labs, John D. Copanos & Co., Biocraft Labs
United Pharm.	Biocraft Labs
The Upjohn Co. Pensyn	Bristol Labs
West-ward	Zenith
Wolins Pharmacal Corp.	See footnote 2

BELLADONNA ALKALOIDS WITH PHENOBARBITAL Tabs

American Pharm. Co.*	American Pharm. Co.
Beecham-Massengill Pharm.	Beecham-Massengill
Canright Corp.*	Anabolic
H.R. Cenci Labs	H.R. Cenci Labs or Zenith Labs
Invenex Pharm.	Invenex Pharm. or Cord Labs
Ladco Labs	Zenith or Richlyn Labs
Lemmon Pharmacal Co.	Lemmon Pharmacal Co.
Eli Lilly & Co.	Eli Lilly & Co.
Parke-Davis & Co.	Parke-Davis & Co.
Penta Products	Halsey Drug Co.
Sheraton Labs	Ketchum Labs
Stanlabs	Stanlabs
Towne, Paulsen & Co.	Towne, Paulsen & Co.
S.J. Turag & Co.*	Cord Labs
United Pharm.	Richlyn Labs
West-ward	West-ward

BENZTHIAZIDE 25, 50 & 60 mg Tabs

Interstate Drug Exchange[4]	Richlyn Labs
Lemmon Pharmacal[4]	Lemmon Pharmacal

BROPHENIRAMINE MALEATE

Elixir (Dimetane)

A.H. Robins Co.*	A.H. Robins Co.

Sustained-Release Tabs (Dimetane Extentabs)

A.H. Robins Co.*	ICN Pharm.

Sustained-Release Tabs with Phenylephrine and Phenylpropanolamine

Barr Labs[1]	Barr Labs
A.H. Robins Co.* Dimetane	ICN Pharm.
Sheraton Labs	Cord Labs

CONTINUED

No response was received from this company. The information listed has been taken from previous articles.

1. Also distributed by Penta Products, under the manufacturer's label.
2. Wolins Pharmacal Corp. responded to our inquiry but declined to provide information as to the actual manufacturer, stating that the products may be obtained from any of a large number of sources.
3. Information supplied by Abbott Laboratories.
4. Information concerning the manufacturer is appropriate only for those dosage strengths distributed by this company.

Manufacturer disclosure

continued

BUTABARBITAL 15 & 30 mg Tabs

Blue Cross[1]	Halsey
Interstate Drug Exchange	Columbia Pharm.
Invenex Pharm.	Invenex Pharm.
McNeil Labs*	McNeil Labs
Stayner Corp.*	Stayner Corp.
Towne, Paulsen & Co.	Towne, Paulsen & Co.
West-ward	West-ward

CALCIUM LACTATE 325 & 650 mg Tabs

American Pharm. Co.*	American Pharm. Co.
Columbia Medical Co.	Bolar Pharm.
Interstate Drug Exchange	Bolar Pharm.
Ladco Labs	West Coast Labs
Eli Lilly & Co.	Eli Lilly & Co.
Parke-Davis & Co.	Parke-Davis & Co.
Penta Products	W.T. Thompson
Rexall Drug Co.*	Rexall Drug Co.
Sheraton Labs	Stayner Corp. or W.T. Thompson Co.
Stanlabs	Stanlabs
Stayner Corp.*	Stayner Corp.
United Pharm.	Northridge Labs
West-ward	West-ward

CHLORAL HYDRATE 500 mg Caps

H.R. Cenci Labs	R.P. Scherer Corp.
Columbia Medical Co.	R.P. Scherer Corp.
ICN Pharm.*	R.P. Scherer Corp.
Invenex Pharm.	R.P. Scherer Corp.
Ladco Labs	R.P. Scherer Corp.
Lederle Labs	R.P. Scherer Corp.
McKesson Labs Kessodrate	R.P. Scherer Corp.
Parke-Davis & Co.	R.P. Scherer Corp.
Penta Products	Chase Chemicals
Philips Roxane Labs	R.P. Scherer Corp.
Progress Labs	R.P. Scherer Corp.
Purepac Pharm. Co.*	R.P. Scherer Corp.
Rexall Drug Co.*	R.P. Scherer Corp.
Sheraton Labs	R.P. Scherer Corp.
Smith Kline & French Labs	R.P. Scherer Corp.
E.R. Squibb & Sons Rocket	R.P. Scherer Corp.
Stanlabs	R.P. Scherer Corp.
Stayner Corp.*	R.P. Scherer Corp.
Towne, Paulsen & Co.	R.P. Scherer Corp.
United Pharm.	R.P. Scherer Corp. or Encapsulations, Inc.
West-ward	R.P. Scherer Corp.
Wyeth Labs*	R.P. Scherer Corp.

CHLORPHENIRAMINE MALEATE 4 mg Tabs

Barr Labs[1]	Barr Labs
H.R. Cenci Labs	H.R. Cenci Labs
Columbia Medical Co.	Barr Labs
Dome Labs	Zenith Labs
Dow Pharm.*	Dow Pharm.
Invenex Pharm.	Invenex Pharm.
Ladco Labs	Zenith Labs
Lederle Labs	Generic Pharm. Corp.
Philips Roxane Labs	Philips Roxane Labs
Progress Labs	Cord Labs
Sheraton Labs	Chromalloy Pharm.
Stanley Drug Prod.	Stanley Drug Prod.
Stayner Corp.*	Stayner Corp.
Towne, Paulsen & Co.	Towne, Paulsen & Co.
United Pharm.	Richlyn Labs
West-ward	West-ward

CHLORPHENIRAMINE MALEATE with PHENYLEPHRINE Liquid

H.R. Cenci Labs	H.R. Cenci Labs
Dow Pharm.*	Dow Pharm.
Progress Labs	Progress Labs
Schering Corp.*	Schering Corp.

CHLORPROMAZINE HCl 25 & 50 mg Tabs

Abbott Labs	Cord Labs
H.R. Cenci Labs	Zenith Labs
Columbia Medical Co.	Zenith Labs
Interstate Drug Exchange	Zenith Labs
Lederle Labs	Western Research Labs
Philips Roxane Labs	Cord Labs
Rachelle Labs	Rachelle Labs
Sheraton Labs	Cord Labs
Smith Kline & French Labs	Smith Kline & French Labs
Stanlabs	Zenith Labs
Stayner Corp.*	Zenith Labs
Towne, Paulsen & Co.	Western Research Labs or Cord Labs
S.J. Tutag & Co.*	Cord Labs
United Pharm.	Richlyn Labs
USV Pharm. Corp.	USV Pharm. Corp.
West-ward	Zenith Labs

APC & CODEINE ⅛, ¼, ½ & 1 gr Tabs

Burroughs-Wellcome Co.*	Burroughs-Wellcome Co.
H.R. Cenci Labs[4]	Zenith Labs
Ladco Labs	ICN Pharm.
Eli Lilly & Co.	Eli Lilly & Co.
Parke-Davis & Co.	Parke-Davis & Co.
Penta Products	Halsey Drug Co.
Sheraton Labs	Cord Labs or Stayner Corp.
Stanlabs	Stanlabs
Stayner Corp.*	Stayner Corp.
Towne, Paulsen & Co.	Towne, Paulsen & Co.
United Pharm.[4]	Halsey Drug Co.

COLCHICINE 0.6 mg Tabs

Abbott Labs	Abbott Labs
H.R. Cenci Labs	Zenith Labs
Columbia Medical Co.	Zenith Labs
Eli Lilly & Co.	Eli Lilly & Co.
Interstate Drug Exchange	Danbury Pharm.
Sheraton Labs	Stayner Corp.
Stanlabs	Stanlabs
Stayner Corp.*	Stayner Corp.
Towne, Paulsen & Co.	Generic Pharm. Corp.
United Pharm.	Barr Labs
West-ward	West-ward

DEXAMETHASONE 0.75 mg Tabs

Barr Labs[1]	Barr Labs
Ciba Pharm. Co.	Ciba-Geigy Corp.
Consolidated Midland Corp.*	Danbury Pharmacal or Cord Labs
Interstate Drug Exchange	Zenith Labs or Danbury Pharm.
Lederle Labs	Barr Labs
Merck Sharp & Dohme	Merck Sharp & Dohme
Organon	Organon
Philips Roxane Labs	Philips Roxane Labs
Rowell Labs	Rowell Labs
Schering Corp.*	Schering Corp.
Sherry Pharm.*	Danbury Pharmacal
Towne, Paulsen & Co.	Towne, Paulsen & Co.
USV Pharm. Corp.	USV Pharm. Corp.
West-ward	West-ward
Zenith Labs*	Zenith Labs

DIGITOXIN 0.1 & 0.2 mg Tabs

Abbott Labs	Abbott Labs
American Pharm. Co.*	American Pharm. Co.
H.R. Cenci Labs[4]	Zenith Labs
Columbia Medical Co.	Zenith Labs
Interstate Drug Exchange	Zenith Labs

* No response was received from this company. The information listed has been taken from previous articles.

1. Also distributed by Penta Products, under the manufacturer's label.
2. Wolins Pharmacal Corp. responded to our inquiry but declined to provide information as to the actual manufacturer, stating that the products may be obtained from any of a large number of sources.
3. Information supplied by Abbott Laboratories.
4. Information concerning the manufacturer is appropriate only for those dosage strengths distributed by this company.

Invenex Pharm.	Invenex Pharm.
Ladco Labs	ICN Pharm.
Lederle Labs	Barr Labs
Eli Lilly & Co.	Eli Lilly & Co.
Parke-Davis & Co.	Parke-Davis & Co.
Philips Roxane Labs	Philips Roxane Labs
Rexall Drug Co.*	Rexall Drug Co.
Towne, Paulsen & Co.	Towne, Paulsen & Co.
S.J. Tuteg & Co.*	Cord Labs
United Pharm.	Barr Labs
West-ward	West-ward

DIGOXIN 0.25 mg Tabs

American Pharm. Co.*	American Pharm. Co.
Burroughs-Wellcome Co.*	Burroughs-Wellcome Co.
H.R. Cenci Labs	Zenith Labs
Columbia Medical Co.	Blue Cross Products
Interstate Drug Exchange	Zenith Labs
Lederle Labs	Barr Labs
Philips Roxane Labs	Philips Roxane Labs
Purepac Pharm. Co.*	Rondex Labs
Rexall Drug Co.*	Rexall Drug Co.
Smith Kline & French Labs	Philips Roxane Labs
Towne, Paulsen & Co.	Towne, Paulsen & Co.
United Pharm.	Barr Labs
West-ward	West-ward

DIPHENHYDRAMINE EXPECTORANT Liquid

H.R. Cenci Labs	H.R. Cenci Labs
Columbia Medical Co.	Bay Labs
Lederle Labs	National Pharm.
Life Labs	Life Labs
McKesson Labs	McKesson Labs
Parke-Davis & Co.	Parke-Davis & Co.
Penta Products	Lile Labs
Progress Labs	Progress Labs
Sheraton Labs	Bay Labs
S.J. Tutag & Co.*	Cord Labs
United Pharm.	National Pharm.

DIPHENHYDRAMINE HCl 25 & 50 mg Caps

Barr Labs[1]	Barr Labs
H.R. Cenci Labs	Zenith Labs
Columbia Medical Co.	Barr Labs or Zenith Labs
Invenex Pharm.	Invenex Pharm.
Ladco Labs	M.D. Pharmaceuticals or Zenith Labs
Lederle Labs	Barr Labs
Lile Labs	Lile Labs
McKesson Labs	McKesson Labs
Parke-Davis & Co.	Parke-Davis & Co.
Philips Roxane Labs	Philips Roxane Labs
Smith Kline & French Labs	Smith Kline & French Labs
Sheraton Labs	Chromalloy Pharm. or Stayner Corp.
Stayner Labs*	Zenith Labs
Towne, Paulsen & Co.	Towne, Paulsen & Co.
S.J. Tuteg & Co.*	Cord Labs
United Pharm.	Barr Labs
West-ward	West-ward

DONNATAL Tabs

A.H. Robins Co.*	A.H. Robins Co.

DOXYCYCLINE HYCLATE 50 mg Caps

Interstate Drug Exchange	Rachelle Labs
Pfizer Labs	Pfizer Labs
Rachelle Labs	Rachelle Labs
United Pharm.	Rachelle Labs
USV Pharm. Corp.	Rachelle Labs

ERYTHROMYCIN BASE 250 & 500 mg Tabs

Abbott Labs	Abbott Labs
Eli Lilly & Co.	Eli Lilly & Co.
McKesson Labs	Reid-Provident
A.H. Robins Co.*	A.H. Robins Co.
The Upjohn Co.	The Upjohn Co.

ERYTHROMYCIN STEARATE 250 mg Tabs

Abbott Labs	Abbott Labs
American Quinine Products*	Zenith Labs
Barr Labs[1]	Barr Labs
Bristol Labs*	Bristol Labs
H. R. Cenci Labs	Zenith Labs
Columbia Medical Co.	Barr Labs
Dow Pharm.*	Barr Labs
ICN Pharm.*	Barre Drug Co.
Ladco Labs	Barr Labs
Lederle Labs	Barr Labs
Mallinckrodt Pharm.*	Mylan Pharm.
Parke-Davis & Co.	Parke-Davis & Co.
Pipharmecs Labs	Pfizer Labs
Philips Roxane Labs	Mylen Pharm.
Rexall Drug Co.*	Mylen Pharm.
Sheraton Labs	Mylan Pharm.
Sherry Pharm.*	Mylan Pharm.
Smith Kline & French Labs	Mylan Pharm.
E. R. Squibb & Sons	E. R. Squibb & Sons
Towne, Paulsen & Co.	Mylan Pharm.
United Pharm.	Barr Labs
West-ward	Zenith Labs
Wyeth Labs*	Mylen Pharm.
Zenith Labs*	Zenith Labs

ESTERIFIED ESTROGENS 0.625, 1.25 & 2.5 mg Tabs

Lederle Labs[4]	Chromalloy Pharm.
Smith Kline & French Labs	Smith Kline & French Labs
Syntex Labs	Syntex Labs

ETHCHLORVYNOL 500 mg Caps

Abbott Labs	Abbott Labs

FENFLURAMINE 20 mg Tabs

A. H. Robins Co.*	A. H. Robins Co.

FERROUS GLUCONATE 325 mg Tabs

American Pharm. Co.*	Inwood Labs
H. R. Cenci Labs	Richlyn Labs
Columbia Medical Co.	Bolar Pharm.
Interstate Drug Exchange	Bolar Pharm.
Invenex Pharm.	Invenex Pharm.
Ledco Labs	Richlyn Labs
Penta Products	Tablicaps
Stanlabs	Stanlabs
Stayner Corp.*	Stayner Corp.
United Pharm.	Richlyn Labs
West-ward	Richlyn Labs

FERROUS SULFATE 325 mg Tabs

American Pharm. Co.*	Tablicaps
H. R. Cenci Labs	Richlyn Labs
Columbia Medical Co.	Tablicaps
Interstate Drug Exchange	Heather Drug Co.
Invenex Pharm.	Invenex Pharm.
Ladco Labs	Richlyn Labs
Eli Lilly & Co.	Eli Lilly & Co.
Parke-Davis & Co.	Parke-Davis & Co.
Penta Products	W. T. Thompson
Philips Roxane Labs	Philips Roxane Labs
Rexall Drug Co.*	Rexall Drug Co.
Sheraton Labs	W. T. Thompson
Smith Kline & French Labs	Smith Kline & French Labs
Stanlabs	Stanlabs
Towne, Paulsen & Co.	Towne, Paulsen & Co.
United Pharm.	Richlyn Labs
West-ward	Standard Labs

FLUOCINOLONE ACETONIDE 0.025% & 0.01% Cream

Syntex Labs	Syntex Labs

GLUTETHIMIDE 0.125, 0.25 & 0.5 gm Tabs

Interstate Drug Exchange[4]	Denbury Pharm. or Zenith Labs
Ledade Labs[4]	Cord Labs
Sheraton Labs	Cord Labs
USV Pharm. Corp.	USV Pharm. Corp.

GLUTETHIMIDE 0.5 gm Caps

USV Pharm. Corp.	USV Pharm. Corp.

CONTINUED

APPENDIX 2

CONGRESS OF THE UNITED STATES
HOUSE OF REPRESENTATIVES
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS
OF THE
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE
WASHINGTON, D.C. 20515

MEMORANDUM:

DATE: August 14, 1978

TO: The Members of the Subcommittee on Oversight and Investigations

FROM: Honorable John E. Moss, Chairman 8/14/78

SUBJECT: Possible Contempt Hearing with HEW Secretary Joseph A. Califano, Jr., on Subpoena No. 95-2-75

At the Subcommittee meeting on July 27, 1978, a subpoena was authorized to the Secretary of the Department of Health, Education and Welfare, Joseph A. Califano, Jr. This subpoena, directed to the Secretary, was served, only after negotiations between the Subcommittee and HEW had broken down, upon F. Peter Libassi, General Counsel of the Department on August 10, 1978. The subpoena requires Secretary Califano to supply the Subcommittee with documents filed by drug manufacturers with the Food and Drug Administration.

The Subcommittee is engaged in an investigation of the regulation of drugs. Included within the scope of this investigation, is the Subcommitte's review of the allegation that a number of drug companies put their trade name on drugs actually manufactured by generic drug companies.

One means to the end of claiming that a drug is manufactured by the trade-name company is for that company to position an employee in the generic drug house while the trade-name product is being manufactured.

The documents we request contain information the manufacturers are required to file with the FDA regarding manufacturing processes, control procedures, and testing methods. Scrutiny of this information is necessary to determine whether there is a difference between the product that is produced under the "man-in-the-plant" as opposed to that product produced by the same generic drug company.

The Subcommittee has made every reasonable attempt to gather the documents without serving the subpoena:

- On July 11, 1978, in a letter (copy attached) hand-delivered to Secretary Califano, the Subcommittee requested documents relating to the "man-in-the-plant" manufacture of drugs.

- On July 20, 1978, Subcommittee staff met with FDA Commissioner Donald Kennedy and his staff. The request for documents was significantly narrowed. For the first time, disclosure of certain documents was questioned by the Commissioner.

- On July 21, 1978, in a letter (copy attached) hand-delivered to Secretary Califano, the Subcommittee again requested documents from the Secretary. This request had been considerably narrowed since the request made on July 11, 1978. This letter has yet to receive a written response.

- Since the letter of July 21, there have been repeated requests for extensions by the Secretary's staff to allow them time to consider submitting the documents to this Subcommittee. This Subcommittee has granted every extension, until it reluctantly served subpoena 95-2-75 on August 10, 1978.

The Secretary has claimed through his staff that he is prohibited by statute [21 U.S.C. 331(j)] from submitting the documents to this Subcommittee. The Subcommittee staff and the Congressional Research Service of the Library of Congress have reviewed the statute (copy attached) and found the Secretary's claim is not supported by the statute's legislative history or by case law.

The Subcommittee's authority to require the production of records identified in subpoena 95-2-75 is clear. The Subcommittee has made every effort to accommodate the Secretary. The Chair will recommend, in absence of compelling evidence in his favor, that Joseph A. Califano, Jr., Secretary of the Department of Health, Education and Welfare, be cited for contempt of Congress if he does not comply with the Subcommittee's demand on August 16, 1978.

Subcommittee staff will be available to brief you or your staff at your convenience.

Attachments

Appendix 3

EXCERPTS FROM WYETH'S FORM 6 FOR THE MANUFACTURER OF AMOXICILLIN TRIHYDRATE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

Form Approved
OMB No. 57-R0009

ANTIBIOTIC APPLICATION

(Check applicable item below)

FORM 5 REQUEST UNDER 146.16 TO PROVIDE FOR CERTIFICATION OF A NEW ANTIBIOTIC OR ANTIBIOTIC-CONTAINING PRODUCT. ☐

FORM 6 DATA TO ACCOMPANY OR PRECEDE EVERY INITIAL REQUEST UNDER 146.2 FOR CERTIFICATION OF AN ANTIBIOTIC DRUG COVERED BY EXISTING REGULATIONS, SECTION 440.103a. ☒

FORM 6 AMENDMENT. REGULATION SECTION _____ IF KNOWN. ☐

FORM 6 AMENDMENT. REGULATION SECTION _____ ☐

FOR USE OF FOOD AND DRUG ADMINISTRATION

DATE APPROVED 4-26-78

ACCOUNT NO.

SIGNED Marvin Seife

FOR THE COMMISSIONER OF FOOD AND DRUGS
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NAME OF APPLICANT
Wyeth Laboratories Inc.

DATE OF APPLICATION
1/10/78

ADDRESS *(Include Zip Code)*
P. O. Box 8299, Philadelphia, Pa. 19101

NAME OF DRUG
Amoxicillin Trihydrate Capsules 250 mg and 500 mg

Commissioner
Food and Drug Administration
Department of Health, Education, and Welfare
Rockville, Maryland 20852

Attention: Certification Services Branch HFD-304

In accordance with regulations promulgated under Section 507 of the Federal Food, Drug, and Cosmetic Act, as amended, we hereby submit this application with respect to an antibiotic product.

Attached hereto, in triplicate (except for the information required under item 9 (a) through (f) which is submitted in single copy) and constituting a part of this application are the following:

1. A full list of the articles used as components of the drug. This list should include all substances used in the fermentation, synthesis, extraction, purification or other method of preparation of any antibiotic and in the preparation of the finished dosage form, regardless of whether they undergo any change or are removed in the process. Each substance should be identified by its established name, if any, or complete chemical name, using structural formulas when necessary for specific identification. If any proprietary preparation is used as a component, the proprietary name should be followed by a complete quantitative statement of composition. Reasonable alternatives for any listed substance may be specified.

2. A full statement of the composition of the drug. The statement shall set forth the name and amount of each ingredient, whether active or not, contained in a stated quantity of the drug in the form in which it is to be distributed, as for example, amount per tablet or per milliliter, and a batch formula representative of that to be employed for the manufacture of the finished dosage form. All components should be included in the batch formula regardless of whether they appear in the finished product. Any calculated excess of an ingredient over the label declaration should be designated as such and percent excess shown. Reasonable variations may be specified.

3. A complete description of the methods and processes used in manufacturing, packing and labeling of the drug to preserve its identity, strength, quality, and purity in conformity with good manufacturing practices including:

(a) Name and location of each plant conducting the operations.

(b) Whether or not each lot of raw materials is given a serial number to identify it, and the use made of such numbers in subsequent plant operations.

(c) Precautions to assure proper identity, strength, quality, and purity of the raw materials, whether active or not, including the specifications for acceptance and methods of testing for each lot of raw material used in the fermentation, synthesis, extraction, and purification of the drug and for each ingredient used in the manufacture of the drug that is to be dispensed.

(d) If it is a drug produced by fermentation:

(i) Source and type of microorganism used to produce the drug.

(ii) Composition of media used to produce the drug.

(iii) Type of precursor used, if any, to guide or enhance production of the antibiotic during fermentation.

(iv) Name and composition of preservative, if any, used in the broth.

(v) A complete description of the extraction and purification processes including the names and compositions of the solvents, precipitants, ion exchange resins, demulsifiers, and all other agents used.

(vi) If the drug is produced by a catalytic hydrogenation process, *(such as tetracycline from chlortetracycline)*, a complete description of the process, including the name of the catalyst used, how it is removed, and how the drug is extracted and purified.

(e) If it is a drug that is synthesized by chemical processes, a detailed description of each chemical reaction with graphic formulas used to produce the drug, including the names and amounts of all substances used in the process.

(NOTE: If the applicant is not the manufacturer of the antibiotic used in making the drug, in lieu of the information required in Xa) through Xe), he should include the name and address of the manufacturer.)

(f) Method of preparation of the master formula records and individual batch records and manner in which these records are used.

(g) Number of individuals checking weight or volume of each individual ingredient entering into each batch of the drug.

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(h) Whether or not the total weight or volume of each batch is determined at any stage of the manufacturing process subsequent to making up the batch according to the formula card, and at what stage and by whom this is done.

(i) At what point in the process the drug is mixed homogeneously and a description of the equipment used for this purpose and its total capacity in terms of pounds, kilograms, gallons, or liters of the drug and the maximum quantity of the drug that is mixed in such equipment.

(j) A description, where applicable, of all equipment used in the fermentation, anytheais, extraction, purification, filtration, sterilizing, grinding, blending, mixing, tableting, encapsulating, filling, packaging, and labeling of the drug.

(k) If it is a sterile drug, a description of the methods used to insure the sterility of each batch and the controls used for maintaining its sterility, including a detailed description of the sterile areas where the drug is produced and packaged.

(l) Additional procedures employed which are designed to exclude contaminants *(e.g., other drug substances, extraneous materials, etc.)* and otherwise assure proper control of the product.

(m) Adequate information with respect to the characteristics of and the test methods employed for the container, closure, or other component parts of the drug container to insure their suitability for the intended use.

(n) Controls used in the packaging and labeling of each batch to insure the standards of identity, strength, quality and purity of the drug.

(o) Precautions to check the total number of finished packages produced from a batch of the drug with the theoretical yield.

(p) Precautions to insure that each lot of the drug is packaged with the proper label and labeling, including provisions for labeling, storage, and inventory control.

(q) Copies of all printed forms used by the applicant in the manufacture, packaging, and labeling of a batch.

(r) The name of each person responsible for each of the above operations and information concerning his scientific training and experience.

4. A complete description of the tests and methods of assay and other controls used during the manufacture of the batch and after it is packaged.

(a) Details of analytical procedures for all active ingredients. The analytical procedures should be capable of determining the active components and of assuring the identity of such components.

(b) Standards used for acceptance of each lot of the finished drug.

(c) A detailed description of the collection of the samples to be tested by the applicant and by the Food and Drug Administration.

(d) Copies of all printed forms used by the applicant in the laboratory control of raw ingredients and the finished batch.

(e) A complete description of the laboratory facilities used in such controls, including:

(i) The location of the laboratory in relation to the plant where the drug is manufactured,

(ii) A description of the laboratory equipment available for performing tests and assays, and

(iii) The names of the persons who will be responsible for conducting the required laboratory tests and information concerning their scientific training and experience.

(f) If the applicant uses the services of a consulting laboratory, the name and address of such laboratory and a statement from such laboratory that includes the information required under 4(a), (b), and (e).

(g) An explanation of the exact significance of any batch numbers used in the manufacturing, processing, packaging, and labeling of the drug, including such control numbers that may appear on the label of the finished article. State whether these numbers enable determination of the complete manufacturing history of the product. Describe any methods used to permit determination of the distribution of any batch if its recall is required.

(h) A complete description of, and data derived from, stability studies of the potency and physical characteristics of the drug, including information showing the suitability of the analytical methods used. Describe any additional stability studies underway or contemplated. Stability data should be submitted for any new antibiotic, for the finished dosage form of the drug in the container including a multiple-dose container in which it is to be marketed, and if it is to be put into solution at the time of dispensing, for the solution prepared as directed.

(i) The expiration date needed to preserve the identity, strength, quality, and purity of the drug until it is used.

5. The following samples shall be submitted with the application or as soon thereafter as they become available:

(a) If it is a new antibiotic: 10 grams of the applicant's reference standard if an official standard has not been designated, plus 5 grams from each of three separate batches. Include for any reference standard a complete description of its preparation and the results of all laboratory tests on it. If the test methods differed from those described in the application, full details of the methods employed in obtaining the reported results shall be submitted.

(b) If it is a dosage form: 6 immediate containers (or 30 tablets or capsules) from each of three separate batches, except that if it is a sterile drug 30 containers shall be submitted from each of three batches.

(c) Include for samples submitted pursuant to items 5(a) or 5(b) detailed results of all laboratory tests made to determine the identity, strength, quality and purity of the batch represented by the sample.

(d) Additional samples shall be submitted on request.

(e) The requirements of items 5(a) or 5(b) may be waived in whole or in part on request of the applicant, or otherwise, when any such samples are not necessary.

6. Each copy of the application shall contain a copy of each label and all other labeling to be used for the drug.

(a) Each label, or other labeling, should be clearly identified to show its position on, or the manner in which it accompanies, the market package.

(b) The labeling on or within the retail package should include adequate directions for use by the layman under all the conditions for which the drug is intended for lay use, or is to be prescribed, recommended, or suggested in any labeling or advertising sponsored by or on behalf of the applicant and directed to laymen.

(c) If the drug is limited in its labeling to use under the professional supervision of a practitioner licensed by law to administer it, its labeling should bear information for use under which such practitioners can use the drug for the purpose for which it is intended, including all the purposes for which it is to be advertised or represented, in accord with 1.106(b) or (c).

(d) If no established name exists for a new antibiotic, the application shall propose a nonproprietary name for use as the established name for the substance.

(e) Typewritten or other draft labeling copy may be submitted for preliminary consideration of an application. An application will not be approved prior to the submission of the final printed label and labeling of the drug. No application may be approved if the labeling is false or misleading in any particular. *(If the article is a prescription drug, copies of proposed advertising may be submitted optionally for comment or approval).*

7. State whether the drug is *(or is not)* limited in its labeling and by this application to use under the professional supervision of a practitioner licensed by law to administer it.

8. It is understood that the labeling, and advertising for the antibiotic drug will prescribe, recommend, or suggest its use only under the conditions stated in the labeling which is part of this application; and if the article is a prescription drug, it is understood that any labeling which furnishes or purports to furnish information for use or which prescribes, recommends, or suggests a dosage for use of the drug will also contain substantially the same information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, any relevant hazards, contraindications, side effects, and precautions, contained in the labeling which is part of this application. It is understood that all representations in this application apply to the drug produced until an amendment providing for a change is approved by the Food and Drug Administration.

9. Full reports of investigations that have been made to show whether or not the drug is safe for use and efficacious in use.

If this is a Form 5 application submit one copy of (a) through (f) below

(a) An application may be found unsatisfactory unless it contains full reports of adequate tests by all methods reasonably applicable to show whether or not the drug is safe and effective for use as suggested in the proposed labeling and includes all the following:

(i) Detailed reports of the preclinical investigations, including studies made on laboratory animals, in which the methods used and the results obtained are clearly set forth. Such information should include identification of the person who conducted each investigation, a statement of where the investigations were conducted, and where the underlying data are available for inspection. The animal studies may not be considered adequate unless they give proper attention to the conditions of use recommended in the proposed labeling for the drug such as, for example, whether the drug is for short - or long - term administration or whether it is to be used in infants, children, pregnant women, or premenopausal women.

(ii) Reports of all clinical tests sponsored by the applicant or received or otherwise obtained by the applicant should be attached. These reports should include adequate information concerning each subject treated with the drug or employed as a control, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, full information concerning any other treatment given previously or concurrently, and a full statement of adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation and a statement of where the underlying data are available for inspection. Ordinarily, the reports of clinical studies will not be regarded as adequate unless they include reports from more than one independent, competent investigator who maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluation of any and all discernible effects attributable to the drug in each individual treated and comparable records on any individuals employed as controls. Except when the disease for which the drug is being tested occurs with such infrequency in the United States as to make testing impractical, some of the investigations should be performed by competent investigators within the United States.

(iii) All information pertinent to an evaluation of the safety and efficacy of the drug received or otherwise obtained by the applicant from any source, including information derived from other investigations or commercial marketing (for example, outside the United States), or reports in the scientific literature, involving the drug that is the subject of the application or pertinent information about any relevantly related drug. An adequate summary may be acceptable in lieu of a reprint of a published article which only supports other data submitted. Include any evaluation of the safety or efficacy of the drug that has been made by the applicant's medical department, expert committee, or consultants.

(iv) If the drug is a combination of previously investigated or marketed drugs an adequate summary of pre-existing information from preclinical and clinical investigation and experience with its components, including all reports received or otherwise obtained by the applicant suggesting side effects, contraindications, and ineffectiveness in use of such components. Such summary should include an adequate bibliography of publications about the components and may incorporate by reference information concerning such components previously submitted by the applicant to the Food and Drug Administration.

(b) An application may be found unsatisfactory unless it includes substantial evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the efficacy of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(c) The complete composition and/or method of manufacture of the drug used in each submitted report of investigation should be shown to the extent necessary to establish its identity, strength, quality, and purity if it differs from the description in item 1, 2, 3, or 4 of the application in any way that would bias an evaluation of the report.

(d) An application shall include a complete list of the names and post office addresses of all investigators who received the drug.

(e) The information required by 9(a) through 9(d) may be incorporated in whole or in part by specific reference to information submitted under the provisions of §130.3.

(f) Explain any omission of reports from any investigator to whom the investigational drug has been made available. The unexplained omission of any reports of investigations made with the drug by the applicant, or submitted to him by an investigator, or the unexplained omission of any pertinent reports of investigations or clinical experience received or otherwise obtained by the applicant from published literature or other sources, that would bias an evaluation of the safety of the drug or its efficacy in use constitutes grounds for finding the application unsatisfactory.

(g) If this is a Form 6 application, in lieu of the information required in 9(a) through 9(f) it should include data adequate to demonstrate that the drug is comparable to the drug for which certification has previously been provided.

10. If this is an amendment, full information on each proposed change concerning any statement made in the approved application. After an application is approved, an amendment may propose changes. An amendment should be submitted for any change beyond the variations provided for in the approved application. An amendment may omit statements made in the approved application concerning which no change is proposed. Any mailing or promotional piece used after the drug is placed on the market is labeling requiring an amendment. An amendment should be submitted for proposed changes in labeling. If a change is made in the components, composition, manufacturing methods, facilities or controls, or in the labeling or advertising from the representations in an approved application and the drug is marketed before an amendment is approved for such change, certification of the drug may be suspended.

Very truly yours,

Wyeth Laboratories Inc.

(Applicant)

Per Joseph N. Bathish

Joseph N. Bathish

Director, Regulatory Affairs

(Indicate Authority)

This application must be signed by the applicant or by an authorized attorney, agent, or official. If the applicant or such authorized representative does not reside or have a place of business within the United States, the application must also furnish the name and post office address of and must be countersigned by an authorized attorney, agent, or official residing or maintaining a place of business within the United States. The data specified under the several numbered headings should be on separate sheets or sets of sheets, suitably identified. The sample of the drug, if sent under separate cover, should be addressed to the attention of the Division of Antibiotics and Insulin Certification and identified on the outside of the shipping package with the name of the applicant and the name of the drug as shown on the application. All applications and correspondence should be submitted in triplicate except for the information required under item 9 (a) through (f) which should be submitted as a single copy attached to the original copy of the application.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

April 28, 1978

Our reference:
G2-120 (440.103a)

Wyeth Laboratories Inc.
Attention: Paul V. Uses
P.O.Box 8299
Philadelphia, Pennsylvania 19101

Gentlemen:

We have completed our review of your Form 6 application dated January 10 1978, amended January 30, 1978 and April 21, 1978, which provides for the batch certification of amoxicillin trihydrate capsules 250 mg. and 500 mg The application as amended is considered to be satisfactory. An approved copy is enclosed for your records.

Your firm is now in a position to request certification of batches of amoxicillin trihydrate capsules 250 mg. and 500 mg., manufactured, contro packaged and labeled at your facilities in Morgantown, West Virginia.

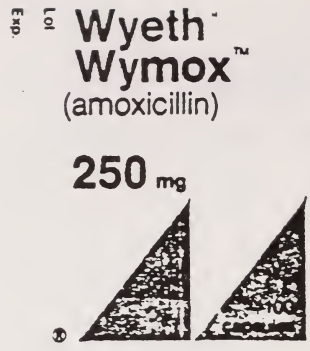
The application as approved provides for a maximum batch size of 3,200,00 250 mg. capsules and 1,600,000-500 mg. capsules. An expiration date of twenty-four months should be used on each batch of the drug submitted for certification Samples from the first three certified batches should be set aside for stability studies. Stability data should be submitted ever six months for the initial twenty-four month expiration period and annual thereafter.

The Form 6 application should be kept up-to-date. Any changes or revisio in the manufacturing process, controls, laboratory procedures or labeling should be submitted as an amendment to the Form 6 application.

Sincerely yours,

Marvin Seife, M.D.
Director
Division of Generic Drug Monographs
Bureau of Drugs

Enclosure



NDC 0008-0559-01

Each capsule contains 250 mg amoxicillin as the trihydrate.

Usual Adult Dosage: One or two capsules every 8 hours.

See enclosed information

Caution: Federal law prohibits dispensing without prescription.

Multiple dispensing package
This package not for household use.

Store at Room Temperature

Made and printed in USA U0559-01-1

WYETH LABORATORIES INC.
Philadelphia, PA 19101

WYETH LABORATORIES INC. Wyeth P.O. Box [illegible] Philadelphia, Pennsylvania

January 10, 1978

Monograph No. 440.103a

Mr. John D. Harrison
Certifiable Drug Review Staff (HFD-535)
Division of Generic Drug Monographs
Bureau of Drugs
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Mr. Harrison:

We request that provision be made under Section 440.103a of the Antibiotic Regulations for certification of Amoxicillin Trihydrate Capsules, 250 mg and 500 mg manufactured by Wyeth Laboratories at Mylan Pharmaceuticals Inc., Morgantown, West Virginia. In support of this request, we are providing herewith the following:

1. The capsules will be manufactured, packaged, and labeled at Mylan's manufacturing laboratory in Morgantown, West Virginia in accordance with the procedures described in Mylan's approved Form 6 No. 62-067. The packaging components used will be those designated in Mylan's approved Form 6.

2. Testing will be done in accordance with the procedures described in Mylan's approved Form 6.

3. Attached herewith are letters from Mylan Pharmaceuticals Inc. authorizing reference by Wyeth Laboratories Inc. to their Antibiotic Master File and approved form 6 No. 62-067. Also attached is a description of the qualifications of the responsible Wyeth employee.

Wyeth

Monograph No. 440.103a

4. Attached herewith is draft copy of the labeling to be used, identical in content to the labeling contained in Mylan's approved Form 6. Final printed labeling will be provided as soon as available.

5. Samples for certification and retention will be collected in accordance with the procedure described in Mylan's Form 6. The expiration date assigned will be 24 months.

6. A control number in the Wyeth format will be assigned each lot of product and will appear on the label of the finished product as well as on the packaging records. Distribution records will be maintained in accordance with Section 429.60 of the Regulations.

We trust that you will find this information satisfactory and that this application may be approved at your earliest convenience.

Sincerely,

WYETH LABORATORIES INC.

Joseph N. Bathish
Director, Regulatory Affairs

JNB:mpd
Enc.

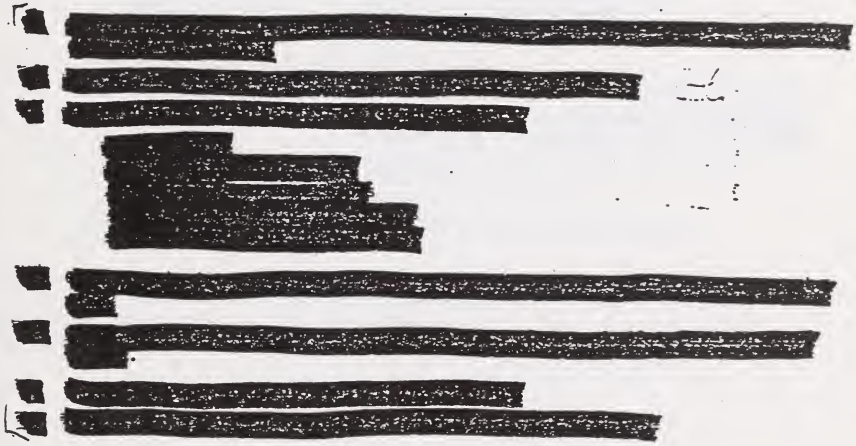
Antibiotic Form 6, Paragraphs 3 and 4

For information required under these paragraphs, please refer to Mylan's approved Form 6 No. 62-067 and Antibiotic Master File dated August 9, 1973. Authorization for reference to these documents is attached herewith.

In addition to the personnel described in Mylan's Master File, Mr. Alex Jones, Manager, Quality Assurance Section, Wyeth Laboratories, Great Valley Laboratory or a designee with a college degree and quality assurance experience, will be present during the production of amoxicillin capsules for Wyeth Laboratories. Mr. Jones' education and experience is listed below:

B.S. Pharmacy	1951
Experience	26 years
Present Position since	1973

The duties and responsibilities of the Wyeth designee at Mylan's Morgantown, West Virginia Laboratory during the production of amoxicillin capsules for Wyeth Laboratories involve the supervision of manufacture and control activities through the responsible Mylan employees. In addition he will perform the following:



ARTICLES USED AS COMPONENTS OF

CAPSULES

AMOXICILLIN TRIHYDRATE, 250 mg AND 500 mg

(FD1675, Antibiotic Form 6, Paragraph 1)

For the information required under paragraph 1, refer to the comparable paragraph in Mylan Pharmaceutical's Form 6 #62-067 for Amoxicillin Trihydrate Capsules.

COMPOSITION OF

CAPSULES

AMOXICILLIN TRIHYDRATE, 250 mg AND 500 mg

(FD 1675 Antibiotic Form 6, Paragraph 2)

For the information required under paragraph 2, refer to the comparable paragraph in Mylan Pharmaceuticals Form 6 #62-067 for Amoxicillin Trihydrate Capsules.

PRECAUTIONS TO ASSURE PROPER IDENTITY, STRENGTH, QUALITY AND PURITY OF THE RAW MATERIALS FOR

AMOXICILLIN TRIHYDRATE CAPSULES

250 mg
500 mg

(FD 1675, Antibiotic Form 6, paragraph 3c)

Please refer to approved Antibiotic Form 6 No. 62-067.

CHARACTERISTICS OF AND THE TEST METHODS FOR

THE CONTAINER, CLOSURE AND OTHER COMPONENT

PARTS OF THE DRUG PACKAGE FOR

CAPSULES

AMOXICILLIN TRIHYDRATE, 250 AND 500 mg

(FD 1675 Antibiotic Form 6 Amendment, Paragraph 3m)

For the information required under paragraph 3m, refer to the comparable paragraph in Mylan Pharmaceutical's Form 6 #62-067 for Amoxicillin Trihydrate Capsules.

DESCRIPTION OF THE TESTS AND METHODS OF ASSAY AND OTHER CONTROLS USED DURING THE MANUFACTURE OF

AMOXICILLIN TRIHYDRATE CAPSULES

250 mg
500 mg

(FD 1675, Antibiotic Form 6, paragraph 4)

Please refer to approved Antibiotic Form 6 No. 62-067.

DATA DERIVED FROM STUDIES OF THE STABILITY OF

CAPSULES

AMOXICILLIN TRIHYDRATE, 250 mg AND 500 mg

(FD 1675, Antibiotic Form 6, Paragraph 4h)

For the information required under paragraph 4h, refer to the comparable paragraph in Mylan Pharmaceutical's Form 6 #62-067 for Amoxicillin Trihydrate Capsules.

APPENDIX 4

FURTHER EXAMPLES OF "MAN-IN-THE-PLANT" ARRANGEMENTS LISTED BY DR. SEIFE IN HIS TESTIMONY

Mr. GORE. We selected one example among what we believe to be many. Can you give us some other examples? I know of one involving Parke-Davis, for example, that I would like to go into in a moment.

Dr. SEIFE. In the nonantibiotic area—I will let Mr. Harrison discuss the antibiotic man-in-the-plant situations—we have several variations on the same sort of theme.

One pure instance of a man-in-the-plant involves a company called Danal Laboratories in St. Louis, Mo., which is now owned by Lemmon Pharmaceuticals of Sellersville, Pa. They have on file an application, an approved application, for the drug imipramine hydrochloride. This product is not made at the Danal premises. It is made by another facility in St. Louis called K.V. Pharmaceuticals. A person from the Danal operation is present when the imipramine is made, imipramine being an antidepressant, at K.V. That is one instance that we have.

A variation of this theme also occurs. We have a firm called Cord Laboratories in Broomfield, Colo. They have two other corporations under the same roof. One is called Tutag Pharmaceuticals. Another is called Geneva Generics. Cord is the manufacturing arm and processes these drugs from start to finish.

Tutag is a corporation which markets brand name drugs, and when the same drug is made by Cord for Tutag, the Tutag corporate structure sends a man over to the Cord facility, and he is there while the drug is made, the brand name drug is made by Cord for Tutag.

Now Geneva Generics is the third example—using the same Cord facility. Geneva Generics is a catalog-type of operation which promotes their generic products to practitioners throughout the country via direct sales. You have the best of all worlds. You have Cord Laboratories making the generic drug, which they sell to distributors who label it for XYZ in California, as well as in different territories around the country. That is one price structure.

You have the brand name Tutag, which you will see in your PDR which I notice on the table. They have a little color section. They do some advertising. They have a small PDR product description section. I assume with the brand name, they have a different price structure. Then you have the direct to the practitioner catalog house, Geneva Generics which is a third price structure. These are is two examples we have come across.

A third example is the Rexall situation in St. Louis. Rexall found themselves making quinidine sulfate, a drug used for cardiac arrhythmias, for their outlets, the Rexall chain throughout the United States. They also made it for other distributors. Subsequently, they found that the Rexall label was being undersold by their distributors for less than the price charged at the Rexall outlets. So they decided there had to be a way around this, and they formed another corporation called Carnegie Laboratories.

Now Carnegie Laboratories filed a separate ANDA—not like Cord. Cord with Geneva Generics and Tutag did not file separate applications. Cord merely submitted their own application.

Mr. GORE. Incorporated by reference.

Dr. SEIFE. And requested that they, Geneva Generics and Tutag, be considered as manufacturers.

What Carnegie did was file a separate new drug application versus the one already approved for Rexall, which we approved.

Now when Carnegie makes the product, they make it at the Rexall facility with the man from the Carnegie corporation. I imagine they might be in the same building, I have no idea, but here we have side by side two forms of quinidine sulfate, both made excellently, both excellent products, but one bearing the Rexall mark, which I assume commands a slightly higher price, and the other competitive with the generic firms bearing the Carnegie mark.

Now those are the three types of nonantibiotics we have come across.

We have had attempts by other firms to get involved with this practice, but we have discouraged them. I think your staff knows of some of these instances and there is no need to go into them because they never reached fruition. We discourage them from doing this.

Now I am speaking only for abbreviated new drug applications and not for full new drug applications, or over-the-counter drugs or anything like that.

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